A method to establish lorazepam milligram equivalent (LME) values for sedative hypnotic medications

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Abstract: Sedative hypnotic medications represent a type of medication that are implicated in a range of adverse outcomes associated with their use, including unintentional overdose death. There is no recognized gold standard equivalency schema that equates potency of these medications as exists with opioid type medications. This paper describes a methodology based on literature search and therapeutic dosing logic to create a comprehensive lorazepam equivalency schema for sedative hypnotic medications used in the United States.

Sedative Overview

Sedative hypnotic (sedative) medications are used broadly in America for numerous medical conditions, including anxiety, seizures, insomnia, muscle relaxation and other conditions where a calming, or a slowing of brain activity is desired. Despite their widespread use, most sedatives can be abused, result in physical dependence, and cause addiction. They also have many other side-effects, such as: dizziness, confusion, sleepiness, increased risk of falls and have a significant potential for dangerous interactions with other drugs. Perhaps the most important side-effect of many sedative medications is respiratory depression, or a slowing or shallowing of breathing. Because of the abuse potential and addictive properties, most sedatives are classified as controlled substances.

There are several types of controlled sedative medications:

- Benzodiazepines – these medications act on the GABA receptor and are very frequently prescribed for anxiety, seizures, and for sleep difficulties. Examples include lorazepam (Ativan), alprazolam (Xanax), and triazolam (Halcion).

- Barbiturates – similar to benzodiazepines in mechanism and use, these drugs also activate the GABA receptor. Examples include secobarbital (Seconal), pentobarbital (Nembutal), and butabarbital (Butisol).

- Z drugs – these medications are nonbenzodiazepine sedatives but have similar effects and partially activate the GABA receptor. They are used primarily for insomnia. Examples include zolpidem (Ambien), zopiclone (Lunesta), and zaleplon (Sonata).

- Gabapentinoids – these medications are often used to treat neuropathic pain. The two primary medications in this class are gabapentin (Neurontin) and pregabalin (Lyrica). Although Pregabalin is a federally controlled drug, gabapentin is not (some states may classify gabapentin as a controlled substance).

- Other – Some drugs, such as surovexant and lacosamide, act on other receptors that control wakefulness and sedation.

Sedative medications are known to have significant potentiating effects when combined with other drugs, such as opioids. Because of the dangers of these drug combinations the CDC has made specific recommendations against the co-prescribing of benzodiazepines and opioids. Research has also shown that Sedatives in general, are frequently implicated in unintentional overdose deaths, especially when co-prescribed with an opioid, as evidenced from this FDA paper, which states:

- Combining opioid pain or prescription opioid cough medicines with medicines called benzodiazepines, which are used for anxiety, insomnia, and seizures, can result in extreme sleepiness, slowed or difficult breathing, coma, or death. These serious side effects result because both opioids and benzodiazepines impact (depress) the central nervous system (CNS). The CNS controls most of the functions of the brain and body.
- These serious side effects can also occur when opioids are combined with other medicines that depress the CNS or alcohol (see List of Prescription Opioid Pain and Cough Medicines, and List of Benzodiazepines and Other CNS Depressants).

  https://www.fda.gov/downloads/Drugs/DrugSafety/UCM518672.pdf

The Need for Dose Equivalents

Sedatives have been repeatedly implicated in unintentional overdose death and studies have reported a dose relationship with risk of overdose. The sedative effect for any medication is based on a number of factors and there is a wide range of resultant milligram doses, ranging from 0.5mg to 450mg or more. Just as with opioids, which are most often equated to morphine to generate a morphine milligram equivalency (MME) value, it is important that sedative dosing also be normalized or equated to a standard to allow for reliable risk modeling. Two common equivalent sedative unit choices are diazepam and lorazepam. Diazepam (Valium) and lorazepam (Ativan) are most often dose equilibrated as 10mg of diazepam = 1mg of lorazepam.

For the purposes of NarxCare, **lorazepam** has been chosen as the comparison sedative for all other sedative medications. Analogous to opioids and their morphine milligram equivalency (MME), sedatives have a corresponding lorazepam milligram equivalency (LME) value.

Sedative Equivalency Literature Review

A literature review was undertaken to establish a range of published equivalency values for sedatives, noting that there is no recognized single standard for sedative equivalencies. Textbook, published research, government reports, manufacturer, and online resources were reviewed to quantify the range of values for each medication.

Determining a final LME value for each medication was accomplished using the following decision tree.

A. If only a single value was found then that value was chosen.
B. If only two values were found then the lowest value was chosen.
C. When more than one value was found, the most common value was chosen, otherwise the lowest published value was chosen
D. If no values were found then an estimate of equivalency was determined through application of logic around therapeutic dosing ranges, with the methodology declared in the table's footnotes.

The following list contains 5 reference sources used to establish dose equivalency ranges for sedatives that are available in the US.

1. **Benzodiazepines: How they work and how to withdraw** (aka the Ashton Manual). Ashton, Heather C. https://www.benzo.org.uk/manual/bzcha01.htm#4

2. **Benzodiazepine equivalents.** Government of South Australia http://www.sahealth.sa.gov.au/wps/wcm/connect/83838b80407711959274ba222b2948cf/Benzodiazepine+equivalents-DASSA-August2014.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-83838b80407711959274ba222b2948cf-m08ay9k

3. **Benzodiazepine Equivalency Table.** Medscape (with associated references) https://emedicine.medscape.com/article/2172250-overview?pa=3lEEoMzTD5eFgkQ4h0Yt%2BXWpAnZL%2BzQTvbZP7bsZi6aPrxRm4Toa9Ctj%2F8UfDkiIVrJxKJt4DRD8mxYr6kYfOw%3D%3D

4. **Benzodiazepine Equivalents.** Family Practice Notebook https://fpnotebook.com/psych/CD/BnzdzpnEqvlnts.htm

5. **Center for Substance Abuse Treatment.** Detoxification and Substance Abuse Treatment. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2006. (Treatment Improvement Protocol (TIP) Series, No. 45.) [Table], Figure 4-6: Other Sedative-Hypnotics and Their Phenobarbital Withdrawal Equivalents. Available from: https://www.ncbi.nlm.nih.gov/books/NBK64116/table/A85650/

Table 1

The following table contains the recommended dose equivalents for each sedative (scaled to lorazepam 1mg) according to the chosen resources. Some drugs were left out of every one of the chosen studies and for those an individualized methodology using available resources was developed to establish an initial equivalency value.

Drug Name	Ref 1	Ref 2	Ref 3	Ref 4	Ref 5	Assigned
amobarbital					0.02	0.02
butabarbital				0.01	0.02	0.01
butalbital					0.01	0.01
mephobarbital					0.008	0.02
pentobarbital				0.01	0.02	0.01
phenobarbital				0.033	0.033	0.033
secobarbital					0.02	0.01
alprazolam	2	1-2	2	2		2
chlorazepate	0.067		0.133			0.067
chlordiazepoxide	0.04		0.1	0.04		0.04
clobazam	0.05	0.05 - 0.033				0.05
clonazepam	2	1-2	4	2		2
diazepam	0.1	0.1	0.2			0.1
estazolam	1 - 0.5					0.5
flurazepam	0.067 - 0.033		0.067	0.067 - 0.133		0.067
halazepam	0.05			0.05		0.05
lorazepam	1	1 - 2	1			1
midazolam						0.2[1]
oxazepam	0.05	0.0167	0.067	0.05		0.05
oxybate						0.0002[2]
quazepam	0.05		0.1			0.05
temazepam	0.05	0.05 - 0.0025	0.1	0.05		0.05
triazolam	2	2	4			2
pregabalin						0.0067[3]
chloral hydrate					0.004	0.004
ethchlorvynol					0.002	0.002
ezogabine						0.01[4]
lacosamide						0.004[5]
meprobamate				0.0025	0.0008	.0008
suvorexant						.02[6]
eszopiclone	0.33					0.33
zaleplon	0.05					0.05
zolpidem	0.05					0.05

Notes:

1. Midazolam dosing established at twice the potency of diazepam. https://ac.els-cdn.com/S0007091217425244/1-s2.0-S0007091217425244-main.pdf?_tid=47c73a45-6f3d-4306-843c-07913f47a96a&acdnat=1523277548_30e6abba7c5545a4902513352749fe82

2. NIH conducted testing of Sodium Oxybate and Zolpidem Tartrate in the treatment of Chronic Insomnia. Oxybate night time dosing stated to be 4.5gm divided compared with zolpidem dosing of 10mg. Given zolpidem 10mg = 0.5mg lorazepam, then 4500mg / 20mg zolpidem = 1 mg lorazepam. https://clinicaltrials.gov/ct2/show/NCT00383643 and https://reference.medscape.com/drug/xyrem-sodium-oxybate-343073

3. The manufacturer conducted a study of recreational users Pregabalin 450mg as equivalent to diazepam 30mg, therefore 150mg Pregabalin = 1 mg lorazepam using established relationships. https://www.pfizermedicalinformation.com/en-us/lyrica/drug-abuse

4. Ezogabine dosing recommended at 300mg per day compared with comparative phenobarbital dosing recommended at 70mg to 210mg per day. Ezogabine potency estimated at 1/3 of phenobarbital

5. Published study evaluating abuse potential of lacosamide equating 800mg to 1.5mg of alprazolam. Alprazolam is twice as potent as lorazepam therefore 3mg lorazepam = 800mg of lacosamide. https://www.ncbi.nlm.nih.gov/pubmed/28926353

6. Published study equating 40mg of surovexant equivalent to 15mg of zolpidem in abuse potential. Zolpidem LME = 0.05 and 0.05 * 15/40 = .01875
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3989084/